Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1245–1255

TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of both enantiomers of γ-ionone, γ-damascone, karahana lactone and karahana ether

Stephen Beszant, Elios Giannini, Giuseppe Zanoni and Giovanni Vidari*

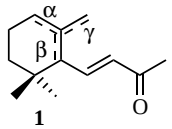
Dipartimento di Chimica Organica, Università di Pavia, Via Taramelli 10, 27100 Pavia, Italy

Received 30 April 2002; accepted 25 June 2002

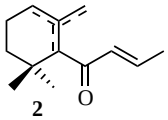
Abstract—A straightforward enantioselective synthesis of both enantiomers of the title compounds is described starting from enantiopure methyl (2*S*,6*R*)- or (2*R*,6*S*)-*cis*-2-hydroxy-γ-cyclogeraniate. These versatile building blocks are obtained by biomimetic cyclization of methyl (6*S*)- or (6*R*)-(*Z*)-6,7-epoxy-7-methyl-3-(trimethylsilyl)methyl-2-octenoate, respectively. The chiral information was encoded by a highly regioselective Sharpless asymmetric dihydroxylation of the corresponding diene.

1. Introduction

Ionones **1** and damascones **2** are among the most important fragrance constituents due to their distinctive fine violet and rose scents.[1,2] Both of these C_{13} norterpenoids exist in nature as three distinct regioisomers, which differ only in the position of the double bond, and are called the α-, β- and γ-isomers.



1
ionones



2
damascones

The γ-isomers are the more difficult to access synthetically, especially in enantiomerically pure form. Indeed, enantiopure γ-ionone **3** has been prepared so far only by means of resolution techniques, either by a classical resolution of menthyl derivatives[3–5] or by an enzymatic kinetic resolution.[6] On the other hand, only one paper describing the synthesis of enantioenriched γ-damascone **4** has appeared in the literature as yet.[7] Olfactory evaluation shows that the regioisomeric purity and the absolute stereochemistry of these compounds dramatically determines the fragrance properties, sometimes with amazingly pronounced differences between the notes and the odor thresholds of the isomers. Furthermore, the exocyclic double bond confers particularly characteristic nuances to the fragrance which can favorably complement other widely used compounds from the same family.[6,7] In this paper we report the first regio- and enantioselective synthesis of γ-ionone not depending on resolution techniques, a new enantioselective synthesis of γ-damascone as well as a straightforward synthesis of karahana lactone **5** and the corresponding ether **6** (Chart 1). Both enantiomers of these precious aroma components can be readily prepared using the same synthetic strategy but changing the stereochemistry of the chiral inducer in the asymmetric step (vide infra). For the sake of conciseness, herein we describe the synthesis of the enantiomers (*S*)-γ-ionone (+)-**3** and (*S*)-γ-damascone (+)-**4**. Indeed, (*S*)-γ-ionone is the most powerful and pleasant odorant of the isomers[6] and (*S*)-γ-damascone is superior to its enantiomer.[7]

2. Results and discussion

Years ago, a few seminal papers by Armstrong and Weiler showed that biomimetic cyclizations of epoxyallylsilanes provide elegant stereo- and regiodefined routes to terpenoid derivatives containing the 1,3-*cis*-disubstituted methylenecyclohexane moiety.[8,9] Later, we were among the first to explore a general regio- and enantioselective approach to these oxirane starting materials by Sharpless asymmetric dihydroxylation (AD) of terpenoid polyenes.[10,11] In this context we envisaged that stereodefined γ-ionone **3** and γ-damascone **4**, as well as stereodefined karahana lactone **5** and

* Corresponding author. Fax: +39 0382507323; e-mail: vidari@chifis.unipv.it

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PII: S0957-4166(02)00335-X

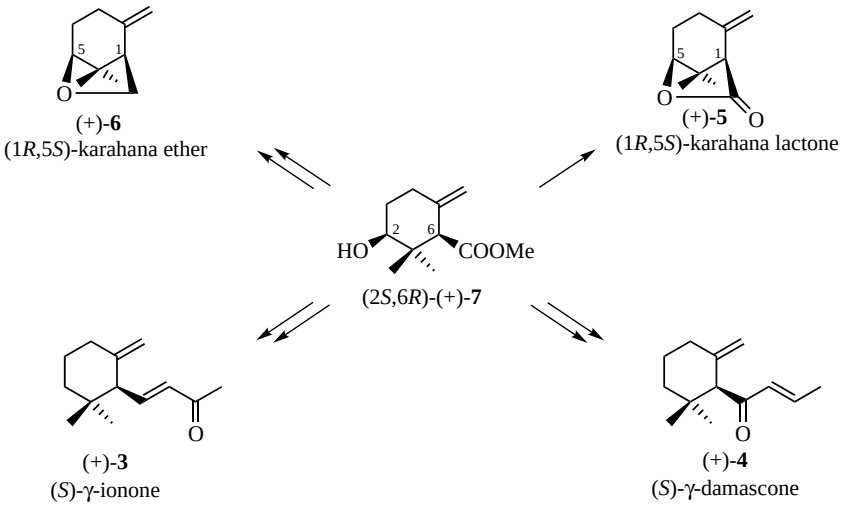


Chart 1.

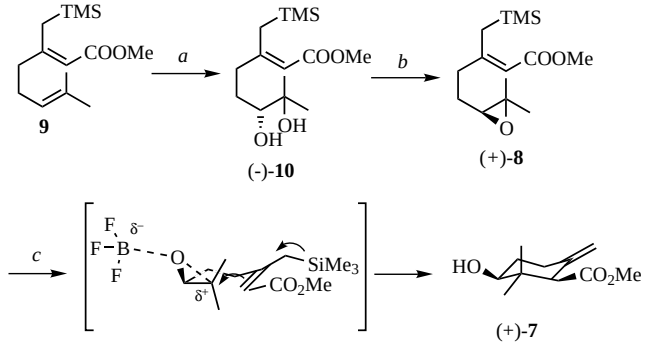
the corresponding ether **6**, could be readily obtained from a common precursor, namely the hydroxy ester **7** which is produced by biomimetic cyclization of the epoxyallylsilane **8**.[8,9]

Both enantiomers of compound **8** are easily obtainable through AD of allylsilane **9** by appropriate choice of the chiral auxiliary (Scheme 1).

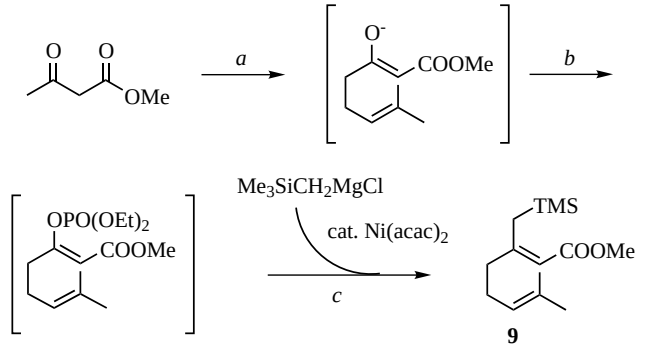
The absolute stereochemistry of product **7** is therefore determined by the absolute stereochemistry of epoxide **8**, while the *cis* orientation of the hydroxyl and the ester groups are dictated by the chairlike conformation of the transition state of the cyclization (Scheme 1). The allylsilane moiety serves both to enhance the reactivity of the substrate and to govern the regioselectivity of the product giving rise to the desired γ isomer.[8,9]

Compounds **7**, **8**, and **9** are, indeed, known compounds; however, **7** and **8** have been described only in a preliminary communication and no experimental or spectroscopic data have been reported.[12] Given the synthetic importance of compounds **7** and **8**, in Section 4 we report their data in full, including the specific optical rotations. In addition, we have markedly speeded up the synthesis of the allylsilane **9**[8,9] which can conveniently be prepared from methyl acetoacetate, 3,3-dimethylallyl bromide, diethylphosphoryl chloride and (trimethylsilylmethyl)magnesium chloride in 51% isolated yield according to our new *one-pot* procedure (Scheme 2). Multigram amounts of pure diene **9** are thus available in just 2 days.

Subsequent dihydroxylation of **9** with AD-mix-β gave diol (−)-**10** in 91% yield and 88% e.e. (Mosher esters) and epoxide (+)-**8** was then obtained in 74% yield according to the Stork procedure.[12] Eventually, BF_3-catalyzed biomimetic cyclization of (+)-**8** gave the key intermediate (+)-**7** in 82% isolated yield and 88% e.e. (enantioselective capillary GC).



Scheme 1. *Reagents and conditions*: (a) AD-mix-β, ^{t}BuOH/H_2O (1:1), 0°C, 22 h, 91%; (b) MsCl (1.1 equiv.), Et_3N (1.1 equiv.), CH_2Cl_2, −40→−20°C, 1 h, then DBU (3 equiv.), 0°C, 3 h, 74% overall; (c) $BF_3{\cdot}Et_2O$ (4 equiv.), CH_2Cl_2, −78°C, 1 h, 82%.



Scheme 2. *Reagents and conditions*: (a) 1. NaH (1.1 equiv.), THF, 0°C, 15 min; 2. BuLi (1.05 equiv.), 0°C, 15 min; 3. 3,3-dimethylallylbromide (1 equiv.), 0°C→rt, 45 min; (b) $(EtO)_2POCl$ (1.05 equiv.), 0°C→rt, 1.5 h; (c) Me_3SiCH_2MgCl 1 M in THF (1.8 equiv.), $Ni(acac)_2$ (0.07 equiv.), 0°C, 1 h, 51% (three steps).

2.1. Enantioselective synthesis of (1*R*,5*S*)-karahana lactone (+)-5 and (1*R*,5*S*)-karahana ether (+)-6

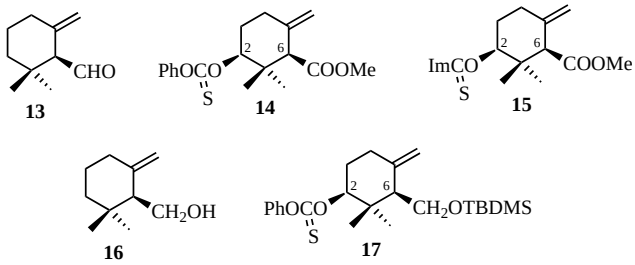
We anticipated that an easy lactonization of **7** to the furanone derivative **5** would result as a consequence of the *cis*-relative configuration of the hydroxyl and carbomethoxy substituents on the cyclohexane ring and conformational equilibrium to the diaxial conformer (Scheme 3). In fact, on treatment with NaH the pleasantly smelling hydroxy ester (+)-**7** was straightforwardly converted into crystalline (+)-karahana lactone **5**, identical with the literature data,[13,14] in 78% isolated yield. Purification by recrystallization from hexane improved the enantiomeric purity of **5** to an e.e. of 96.7% (enantioselective capillary GC). Compound **5** has already been the subject of two enantioselective syntheses;[13,14] however, contrarily to our route, these approaches were based on biocatalyzed reactions.

Karahana lactone **5** was previously converted to karahana ether **6** via the *cis*-diol **11**.[9,14] We explored an alternative route, based on a slightly modified Rychnovsky procedure for the conversion of esters into ethers,[15] which allowed the previously installed furan ring to be preserved. Thus, reduction of enantioenriched (+)-**5** with DIBALH (1 equiv.) in toluene at −78°C and subsequent treatment with DMAP (1.1 equiv.), pyridine (3 equiv.) and Ac_2O (4 equiv.) with slow heating to rt, furnished, after 14 h, an anomeric mixture of karahana lactol-acetate **12** in 82% isolated yield. Finally, on exposure to BF_3 (2.5 equiv.) and Et_3SiH (5 equiv.) in CH_2Cl_2 at −78°C compound **12** smoothly afforded the highly volatile (+)-karahana ether, (+)-**6**, as a colorless liquid with a pleasant camphor-like odor in 80% yield. The spectral data of **6** were in complete agreement with those reported in the literature.[13,14]

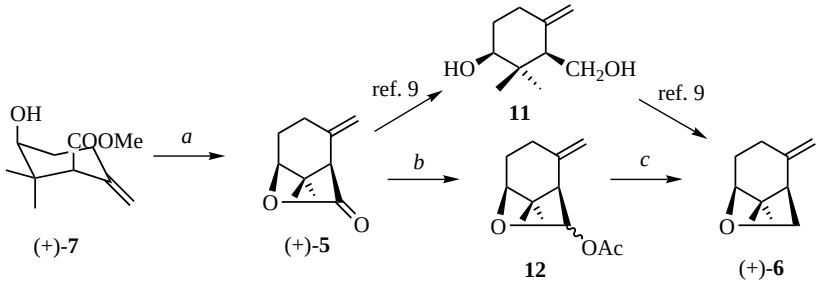
In conclusion, karahana lactone (+)-**5** and the corresponding ether (+)-**6** were prepared from readily available starting materials in only five steps and 22% overall yield and eight steps and 14% overall yield, respectively, with excellent diastereomeric purities. Compounds **5** and **6** are monoterpenoid components of the Japanese hop, *Humulus lupulus* L.[16] In addition, Monti et al. have recently demonstrated the utility of **5** as an enantiopure building block in the synthesis of elegansidiol.[17]

2.2. Enantioselective synthesis of (*S*)-γ-ionone (+)-3 and (*S*)-γ-damascone (+)-4

While the integrity of the C(6) stereochemistry of hydroxy ester **7** was of no concern in its conversion into lactone **5** due to conformational constraint, it became our main issue in the synthesis of (*S*)-γ-ionone (+)-**3** and (*S*)-γ-damascone (+)-**4**, from (+)-**7**. Indeed, we envisaged the synthesis of both isomeric ketones **3** and **4** by appropriate C_3-elongations of γ-cyclocitral **13** which, in principle, could be obtained by deoxygenation at C(2) and reduction of the C(6) ester group of compound **7**.



Among the very few procedures described in the literature for the deoxygenation of hindered secondary alcohols structurally related to compound **7**, Barton-like radical deoxygenation reactions[18] are by far the most commonly employed methods.[19,20] Rather unexpectedly, in our hands, the success of the reaction proved to be sensitive to the type of substituents at C-2 and C-6 of the dimethylcyclohexane moiety. Thus, either the phenoxythiocarbonate **14**† or the imidazoylthiocarbonate **15**‡ on exposure to Bu_3SnH and catalytic AIBN in toluene at reflux, followed by reduction in situ with $LiAlH_4$, afforded the desired γ-cyclogeraniol (+)-**16** in about 30% yield. Similarly, radical deoxygenation of



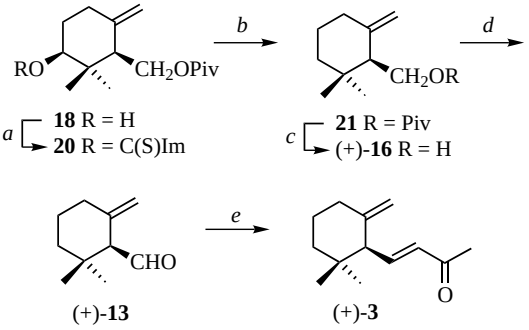
Scheme 3. *Reagents and conditions*: (a) NaH (1.05 equiv.), THF, 0°C, 2 h; crystallization, 78%; (b) 1. DIBALH (1 equiv.), toluene, −78°C, 45 min; 2. Py (3 equiv.), DMAP (1.1 equiv.), Ac_2O (4 equiv.), −78°C→rt, 14 h, 82%; (c) Et_3SiH (5 equiv.), $BF_3{\cdot}Et_2O$ (2.5 equiv.), CH_2Cl_2, −78→−60°C, 1 h, 80%.

† **7**, PhOC(S)Cl (2 equiv.), Py (4 equiv.), CH_2Cl_2, rt, 6 h, yield = 95%.
‡ **7**, $Im_2C{=}S$ (2 equiv.), toluene, reflux, 18 h, yield = 91%.

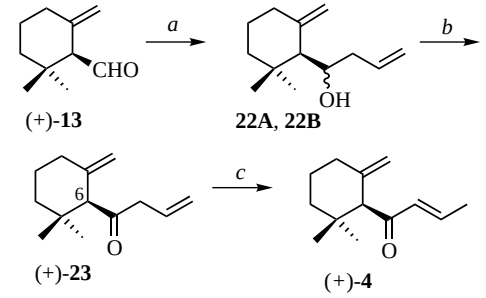
phenoxythiocarbonate **17**[§] followed by silyl ether cleavage with Bu_4NF, met with limited success, giving alcohol **16** in only 40% yield. The carbomethoxy, as well as the TBDMS group appeared to interfere to some extent with the radical deoxygenation of compounds **14**, **15**, and **17**, respectively.

Consequently, with the expectation that a hindered ester protecting group could be more stable to radical species, diol **11** was exposed to pivaloyl chloride (1.1 equiv.) in CH_2Cl_2–pyridine (1:1) at 0°C in order to prepare the primary pivaloate **18** (Scheme 4). In the event, a ca. 7:3 (TLC) mixture of monoprotected esters **18** and **19** was formed after 1 h at 0°C, regardless of the apparently different steric accessibility of the two hydroxyl groups of compound **11**; however, subsequent in situ intramolecular equilibration at room temperature slowly enriched the mixture in the thermodynamically more stable pivaloate (−)-**18** (Scheme 4). Chromatographically pure ester **18** was converted into imidazoylthiocarbonate **20**, which was cleanly deoxygenated to pivaloate **21** under standard conditions. Reduction of compound **21** afforded the long sought (*S*)-γ-cyclogeraniol (+)-**16** uneventfully (Scheme 5). Oxidation of (+)-**16** using the Swern protocol[21] furnished (*S*)-γ-cyclocitral (+)-**13** in 86% isolated yield, which had identical spectral data to that reported in the literature.[7] C_3-elongation of this readily epimerizable, base sensitive aldehyde to diastereomerically and regioisomerically pure (GC) (*S*)-γ-ionone (+)-**3**, $[\alpha]_D^{20} = +30.3$ (*c* 1.1, CH_2Cl_2), was effected straightforwardly and cleanly with the barium-hydroxide-promoted modification[22] of the Horner–Wadsworth–Emmons (HWE) reaction in 81% yield. The spectral data of our synthetic sample were in complete agreement with the literature;[6] moreover, GC analysis on an enantioselective capillary column showed an e.e. of 88%, indicating a completely enantiospecific conversion of (+)-**7** into (+)-**3**.

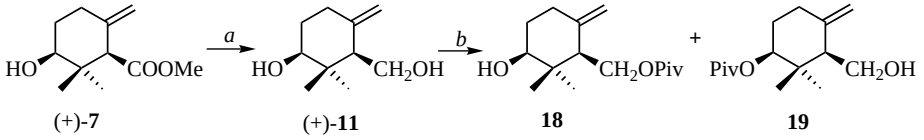
Synthesis of (*S*)-γ-damascone (+)-**4** was the last target of our synthetic plan. To secure this valuable fragrance constituent we envisioned an alternative elongation of γ-cyclocitral (+)-**13** through nucleophilic allylation of the carbonyl group (Scheme 6). Allylations of aldehyde **13** with allyltrimethylsilane under Sakurai reaction conditions[23,24] or with the more reactive allyltributyltin[25,26] were the methods of choice to prevent base-catalyzed enolization of the carbonyl group, which was expected to occur with allyllithium or magnesium derivatives. After some experimentation the highest efficiency was achieved with the tin reagent. Thus, slow addition of BF_3 (1 equiv.) to a mixture of (*S*)-γ-cyclocitral (+)-**13** (1 equiv.) and excess allyltributyltin (3 equiv.) smoothly furnished epimeric adducts **22A** and **22B** (undetermined stereochemistry at the carbinol center) as a ca. 56:44 mixture (GC). Subsequent oxidation of alcohols **22A**–**B** using the Dess–Martin periodinane[27] gave (+)-**23** in 71% overall yield (2 steps). This ketone was immediately exposed to a hindered base with the expectation that double-bond conjugation to (*S*)-γ-damascone (+)-**4** would occur



Scheme 5. *Reagents and conditions*: (a) Im_2CS (2.5 equiv.), toluene, 110°C, 14 h, 92%; (b) Bu_3SnH (5 equiv.), cat. AIBN, toluene, 110°C, 26 h; (c) $LiAlH_4$ (8 equiv.), 0°C, 1.5 h, 75% overall; (d) Swern oxidation, 86%; (e) $Ba(OH)_2{\cdot}8H_2O$ (0.6 equiv.), $(EtO)_2P(O)CH_2COCH_3$ (3 equiv.), THF/H_2O 40:1, 15 h, 81%.



Scheme 6. *Reagents and conditions*: (a) $Bu_3SnCH_2CH{=}CH_2$ (3 equiv.), $BF_3{\cdot}Et_2O$ (1 equiv.), CH_2Cl_2, −78°C, 30 min; (b) Dess–Martin periodinane[27] (1.2 equiv.), CH_2Cl_2, rt, 1.5 h, 71% (two steps); (c) DBU (0.5 equiv.), CH_2Cl_2, rt, 7 h, 90%.



Scheme 4. *Reagents and conditions*: (a) $LiAlH_4$ (2.5 equiv.), THF, 0°C, 2 h, 99%; (b) PivCl (1.1 equiv.), CH_2Cl_2–Py (1:1), 0°C→25°C, 18 h, 70% **18** from **11**.

[§] (a) **11**, TBDMSCl (1.1 equiv.), Im (1.5 equiv.), DMAP (0.3 equiv.), CH_2Cl_2, rt, 4 h, yield = 99%; (b) PhOC(S)Cl (2 equiv.), Py (4 equiv.), CH_2Cl_2, rt, 4 h, yield = 98%.

without concomitant appreciable erosion of the C(6) stereochemistry. In the event, double bond isomerization promoted by catalytic DBU proceeded smoothly at room temperature, affording (*S*)-γ-damascone (+)-**4**, $[\alpha]_D^{20}=+230$ (*c* 1.40, CH_2Cl_2), in 90% yield and with complete conservation of the optical purity (87.5% e.e. by enantioselective HPLC). The ^1H NMR and GC analysis of **4** revealed a mixture of *E*/*Z* olefins whose ratio was depending on reaction time and base amount, changing from 24:1 after 7 h to 50:1 after 18 h with 0.5 equiv. of DBU. The IR and NMR data of the major diastereomer were fully consistent with those of γ-damascone reported in the literature.[28]

3. Conclusion

In conclusion, an enantiospecific synthesis of (*S*)-γ-ionone (+)-**3**, (*S*)-γ-damascone (+)-**4**, (1*R*,5*S*)-karahana lactone (+)-**5**, and (1*R*,5*S*)-karahana ether (+)-**6** was accomplished starting from a common precursor, hydroxy ester (+)-**7**, which was readily available by biomimetic cyclization of epoxide (+)-**8**. This represents the first enantioselective synthesis of γ-ionone not depending on resolution techniques, the second enantioselective synthesis of γ-damascone, and a very convenient route to enantioenriched karahana lactone and the corresponding ether. Moreover, the opposite series of enantiomers is easily at hand by using (−)-**7** as the starting material. In fact, this compound is readily available through AD of diene **9** (Scheme 1) with the opposite AD mixture, AD-mix-α.

4. Experimental

Tetrahydrofuran, diethyl ether and toluene were distilled from sodium/benzophenone; pyridine and methylene chloride were distilled over calcium hydride. All the solvents were distilled under an argon atmosphere. Commercially available reagents were used as supplied without further purification, except for methanesulfonyl chloride and triethylamine, which were distilled over calcium hydride under an argon atmosphere prior to use. All the reactions were performed in glassware that had been dried in an oven at 140°C for at least 3 h prior to use and allowed to cool in a desiccator over self-indicating silica gel pellets. Syringes and needles for the transfer of reagents were dried at 140°C and allowed to cool in a desiccator over P_2O_5 before use. The reactions were carried out under a slight positive static pressure of argon. Routine monitoring of reactions was performed using GF-254 Merck (0.25 mm), aluminum-supported TLC plates. Compounds were visualized by UV irradiation at a wavelength of 254 nm, or stained by exposure to a 0.5% solution of vanillin in H_2SO_4–EtOH followed by charring. Flash column chromatography was performed using Kieselgel 60 Merck (40–63 μm). Yields are reported for chromatographically and spectroscopically pure isolated compounds. Melting points were carried out on an Electrothermal Fisher–Johns apparatus and are uncorrected. Optical rotation measurements were obtained with a Perkin–Elmer 241 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded with a Finnigan Mat 8222 instrument using the electron impact ionization technique (70 eV, 0.5 mA). Electrospray mass spectrometry was carried out using a Thermo Finnigan LCQ-DECA instrument. ^1H NMR (300 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded in $CDCl_3$ solution with a Bruker CXP 300 spectrometer. Chemical shifts are reported in δ units relative to $CHCl_3$ [δ_H 7.26, δ_C (central line of t) 77.0]; the abbreviations s = singlet, d = doublet, t = triplet, q = quartet, qu = quintuplet, m = multiplet, and br = broad are used throughout. Coupling constants (*J*) are given in Hz. The multiplicity (in parentheses) of each carbon atom was determined by DEPT experiments. Infra-red absorption spectra were recorded on FT-IR Perkin–Elmer Paragon 100 PC spectrophotometer in the range of 4000–600 cm^{-1}. GC analyses were carried out with a Hewlett–Packard 5890 II instrument on a HP-5 column (25 m, 0.25 mm i.d., 0.33 μm f.t., N_2 carrier gas: 50 kPa) with the following temperature program: 80°C (3 min)→7°C/min→140°C (0 min)→10°C/min→250°C (0–10 min). Enantiomeric excesses (e.e.) were determined with the following techniques: (i) enantioselective GC analysis on a β-Dex 110 column (30 m, 0.25 mm i.d., 0.25 μm f.t, He carrier gas) mounted on a Hewlett–Packard 5890 II chromatograph for compound **7**; (ii) enantioselective GC analysis on a DMePeBETACDX column (25 m, 0.25 mm i.d., 0.25 μm f.t., 'EasySep' purchased from Analytical Technologies; He carrier gas) mounted on a Hewlett–Packard 5890 II chromatograph for γ-ionone **3**; (iii) enantioselective GC analysis using a DAcTBuSilBETACDX column (25 m, 0.32 mm i.d., 0.25 μm f.t., 'EasySep' purchased from Analytical Technologies; He carrier gas) mounted on a Hewlett–Packard 5890 II instrument for karahana lactone **5**; (iv) enantioselective HPLC analysis on a Daicel Chiralcel® OD 4.6×250 mm column mounted on a Waters HPLC instrument (pump: Waters 515, UV–Vis detector: Waters 409E (454 nm)) for γ-damascone

4.1. Methyl (*Z*)-7-methyl-3-(trimethylsilyl)methyl-2,6-octadienoate, 9

A solution of methyl acetoacetate (9.3 mL, 85.9 mmol) in dry THF (50 mL) was added dropwise to NaH (60% dispersion in mineral oil, 3.78 g, 1.1 equiv.) in dry THF (100 mL) at 0°C. After complete addition, the solution was stirred at the same temperature for 15 min, then BuLi (2.5 M solution in hexanes, 36.1 mL, 1.05 equiv.) was added dropwise and the mixture was stirred at 0°C for further 15 min. 3,3-Dimethylallylbromide (10 mL, 85.9 mmol, 1 equiv.) was then added and the mixture was allowed to warm to room temperature (45 min). The mixture was then cooled to 0°C, diethylchlorophosphate (12.8 mL, 1.05 equiv.) was added dropwise, and the resulting enolphosphate was stirred for 1.5 h while warming to rt. In a separate flask Me_3SiCH_2MgCl was prepared from Me_3SiCH_2Cl (1 M in THF, 21.6 mL, 1.8 equiv.) and Mg (3.86 g, 1.85 equiv.) in dry THF (160 mL) at 0°C, and to it was added $Ni(acac)_2$ (1.63 g, 0.07 equiv.), followed after 15 min by the mixture of the enolphosphate. After com-

plete addition (30 min) the mixture was kept for 1 h at 0°C and then poured into a mixture of 1 M aq. HCl and Et_2O at 0°C; the phases were separated and the organic layer was washed with a further portion of 1 M aq. HCl. The aq. phase was extracted with Et_2O (×3) and the organic layer washed with brine (×3), dried over Na_2SO_4 and evaporated. The crude extract was purified by silica gel chromatography (hexane→hexane:EtOAc, 98:2) to give ester **9**[9] as a pale yellow oil (11.1 g, 51% overall yield); IR (neat): *ν* 1714; 1626; 1434; 1248; 1157; 849; ^{1}H NMR: *δ* 0.04 (s, 3×3H, Me_3Si), 1.60 and 1.68 (2s, 2×3H, CMe_2), 1.99–2.17 (m, 4H, C(4)H_2 and C(5)H_2), 2.41 (s, 2H, CH_2Si), 3.65 (s, 3H, COO*Me*), 5.08 (s, 1H, C(2)*H*), 5.54 (t, *J*=6.3 Hz, 1H, C(6)*H*); ^{13}C NMR: *δ* 1.0 (Me_3Si), 17.5 and 25.4 (C(7)Me_2), 25.9, 26.4 and 40.4 (*C*(4), *C*(5) and *C*H_2TMS), 50.3 (COO*Me*), 110.8 (*C*(6)), 122.9 (*C*(2)), 132.3 (*C*(7)), 164.2 and 167.5 (*C*(3) and *C*(1)); EIMS: *m*/*z* (%) 254 [M$^+$] (9), 239 (46), 223 (40), 211 (5), 195 (6), 186 (12), 171 (22), 150 (35), 135 (21), 122 (12), 121 (11), 107 (78), 89 (21), 82 (51), 73 (100), 69 (26), 59 (11), 45 (23), 41 (38).

4.2. Methyl (6*R*)-(*Z*)-6,7-dihydroxy-7-methyl-3-(trimethylsilyl)methyl-2-octenoate, (−)-10

AD-mix-β (25g, 2.1 g/mmol) and $MeSO_2NH_2$ (1.19, 1.05 equiv.) were added to a mixture of diene **9** (3.04 g, 11.9 mmol) in H_2O–^{t}BuOH (1:1, 240 mL) at 0°C, and the mixture was vigorously stirred at 0°C for 22 h and then quenched with sodium metabisulfite. The mixture was stirred at rt for 30 min, diluted with abundant H_2O and CH_2Cl_2, and the phases were separated. The aq. layer was extracted with CH_2Cl_2 (×3) and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue of ^{t}BuOH was evaporated as its azeotrope with hexane. The crude extract was purified by silica gel chromatography (hexane-EtOAc, 8:2→7:3) to give diol (−)-**10** as a viscous pale yellow oil (3.11 g, 91% yield, 88% e.e. determined with Mosher esters); $[\alpha]_D^{20}=-7.50$ (*c* 1.1, CH_2Cl_2); IR (neat): *ν* 3435; 2955; 2928; 2856; 1713; 1694; 1622; 1435; 1372; 1249; 1159; 1077; 1030; 941; 844; 773; 697; 641; ^{1}H NMR: *δ* 0.04 (s, 3×3H, Me_3Si), 1.15 (s, 3H, *Me*C(7)Me), 1.20 (s, 3H, MeC(7)*Me*), 1.44–1.73 (m, 2H, C(4)H_2), 1.72 (s, 1H, C(7)O*H*), 2.07–2.17 and 2.34–2.40 (2m, 2×1H, C(5)H_2), 2.16 (d, *J*=4.4 Hz, 1H, C(6)*OH*), 2.31 and 2.55 (ABq, *J*=11.2 Hz, 2H, Me_3SiCH_2), 3.35 (ddd, *J*=2.2, 4.4, 6.6 Hz, 1H, C(6)*H*), 3.64 (s, 3H, COO*Me*), 5.55 (s, 1H, C(2)*H*); ^{13}C NMR: *δ* −0.9 (Me_3Si), 23.2 and 25.5 (Me_2C(7)), 25.1 and 29.9 (*C*(4) and *C*(5)), 37.5 (*C*H_2TMS), 50.5 (COO*Me*), 73.0 (*C*(7)), 77.7 (*C*(6)), 111.1 (*C*(2)), 164.3 (*C*(3)), 167.5 (*C*(1)). Anal. calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78; O, 22.19; Si, 9.74. Found: C, 58.41; H, 9.83%.

4.3. Methyl (6*S*)-(*Z*)-6,7-epoxy-7-methyl-3-(trimethylsilyl)methyl-2-octenoate, (+)-8

Et_3N (1.8 mL, 1.1 equiv.), followed by MsCl (1 mL, 1.1 equiv.), was added dropwise to a solution of diol (−)-**10** (3.437 g, 11.9 mmol) in dry CH_2Cl_2 (120 mL) at −40°C. The solution was kept between −40 and −20°C for 1.5 h, then warmed to 0°C, and DBU (5.3 mL, 3 equiv.) was added. After 3 h satd aq. $NaHCO_3$ was added; the aqueous phase was extracted with CH_2Cl_2 (×3) and the combined organic layers were washed with satd aq. $CuSO_4$ (×2) and brine, dried (Na_2SO_4) and evaporated. The crude residue was purified by chromatography on silica gel (hexane–EtOAc, 95:5) to afford epoxide. (+)-**8** (2.39 g, 74% yield); $[\alpha]_D^{20}=+0.5$ (*c* 2.78, CH_2Cl_2); IR (neat): *ν* 2955; 1713; 1626; 1434; 1378; 1248; 1234; 1189; 1160; 1028; 844; 695; 637; ^{1}H NMR: *δ* 0.06 (s, 3×3H, Me_3Si), 1.26 (s, 3H, *Me*C(7)Me), 1.30 (s, 3H, MeC(7)*Me*), 1.68–1.75 (m, 2H, C(5)H_2), 2.13–2.30 (m, 2H, C(4)H_2), 2.37 and 2.49 (ABq, *J*=11.2 Hz, 2H, Me_3SiCH_2), 2.71 (t, *J*=6.1 Hz, 1H, C(6)*H*), 3.66 (s, 3H, COO*Me*), 5.56 (s, 1H, C(2)*H*); ^{13}C NMR: *δ* −1.0 (Me_3Si), 18.6 and 24.7 (Me_2C(7)), 26.1 and 27.4 (*C*(4) and *C*(5)), 37.2 (*C*H_2TMS), 50.5 (COO*Me*), 58.4 (*C*(7)), 63.4 (*C*(6)), 111.3 (*C*(2)), 164.2 (*C*(3)), 167.4 (*C*(1)); EIMS: *m*/*z* (%) 270 [M$^+$] (2), 255 (9), 239 (3), 223 (2), 211 (3), 195 (5), 181 (8), 166 (8), 149 (18), 121 (50), 107 (9), 95 (32), 89 (25), 82 (19), 73 (100), 67 (16), 59 (17), 45 (16), 43 (20), 41 (16). Anal. calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69; O, 17.75; Si, 10.39. Found: C, 62.25; H, 9.75%.

4.4. Methyl (1′*R*,3′*S*)-3′-hydroxy-2′,2′-dimethyl-6′-methylene-1′-cyclohexylcarboxylate (methyl (2*S*,6*R*)-(+)-*cis*-2-hydroxy-γ-cyclogeraniate), (+)-7

$BF_3{\cdot}Et_2O$ (4 equiv.) was added dropwise to a solution of epoxide (+)-**8** (2.89 g, 10.7 mmol) in dry CH_2Cl_2 (110 mL) at −78°C and the solution was stirred at −78°C for 1 h. The reaction was then quenched with satd aq. $NaHCO_3$ and the mixture was stirred at rt for 30 min. The organic layer was washed with a further portion of satd aq. $NaHCO_3$ and the aq. phase was extracted with CH_2Cl_2 (×3). The combined organic layers were then washed with brine, dried (Na_2SO_4) and evaporated. The crude residue was purified by chromatography on silica gel (hexane-EtOAc, 95:5→80:20) to give 1.75 g (82% yield) of ester (+)-**7**;[12] $[\alpha]_D^{20}=+109$ (*c* 0.78, CH_2Cl_2); 88% e.e.{enantioselective GC on a β-Dex 110 column; temperature program=100°C (3 min)→5°C/min→190°C (5 min); $t_R=16.9$ min for (−)-**7** and 17.2 min for (+)-**7**)}; IR (neat): *ν* 3432; 2948; 1741; 1708; 1649; 1437; 1357; 1251; 1211; 1155; 1131; 1073; 1027; 950; 900; 853; 781; 664; ^{1}H NMR: *δ* 0.96 and 1.07 (2s, 2×3H, Me_2C(2′)), 1.79–1.85 (m, 2H, C(4′)H_2), 2.06–2.14 (dt, *J*=4.8, 14.0 Hz, 1H, *H*C(5′)H), 2.49–2.60 (m, 1H, *H*C(5′)H), 2.99 (s, 1H, C(1′)*H*), 3.36–3.42 (m, 1H, C(3′)*H*), 3.68 (s, 3H, COO*Me*), 4.42 (d, *J*=10.1 Hz, 1H, CHO*H*), 4.82 and 4.93 (2 br s, 2×1H, =CH_2); ^{13}C NMR: *δ* 18.1 and 23.1 (C(2′)Me_2), 22.5 and 26.5 (*C*(4′) and *C*(5′)), 34.1 (*C*(2′)), 49.0 (*C*(1′)), 55.4 (COO*Me*), 70.2 (*C*(3′)), 109.0 (=*C*H_2), 138.5 (*C*(6′)), 175.1 (*C*(1)); EIMS: *m*/*z* (%) 198 [M$^+$] (21), 181 (20), 180 (13), 165 (5), 155 (3), 139 (10), 138 (11), 137 (8), 121 (100), 105 (20), 95 (36), 93 (18), 91 (16), 81 (18), 79 (28), 77 (16), 67 (31), 59 (8), 55 (15), 43 (29), 41 (23). Anal. calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; O, 24.21. Found: C, 66.81; H, 9.22%.

4.5. (1*R*,5*S*)-8,8-Dimethyl-2-methylene-6-oxabicyclo-[3.2.1]octan-7-one ((1*R*,5*S*)-(+)-karahana lactone), (+)-5

NaH (60% dispersion in mineral oil, 28.6 mg, 1.05 equiv.) was added in small portions over 5 min to a solution of (+)-**7** (135 mg, 0.681 mmol) in dry THF (7 mL) at 0°C. The mixture was stirred at 0°C for 2 h, then the reaction was quenched with satd aq. NH_4Cl. After dilution with Et_2O and separation of the phases, the aq. phase was extracted with Et_2O (×3); the organic layer was then washed with satd aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated. The crude residue was recrystallized from hexane (0.5 mL) by progressive cooling (rt, 0°C, −20°C) to give (+)-karahana lactone (+)-**5** as colorless needles (87.8 mg, 78% yield); mp 38–41°C; 96.7% e.e. {enantioselective GC on a DAcTBuSilBETACDX column; He gas carrier, 1.27 mL/min; split ratio = 1:36; temperature program = 120°C (1 min), 1°C/min→135°C (0 min), 5°C/min→150°C (0 min); t_R = 15.0 min for (+)-**5** and 15.8 min for (−)-**5**); $[\alpha]_D^{20}$ = +260.5 (*c* 0.90, CH_2Cl_2), [lit. $[\alpha]_D$ = −236.0 (*c* 0.83, $CHCl_3$)[13] and $[\alpha]_D^{25}$ = −295.0 (*c* 1.0, $CHCl_3$)[14] for (−)-**5**]; IR (KBr): *ν* 2963, 1772, 1648, 1395, 1373, 1341, 1293, 1252, 1199, 1139, 1059, 1033, 991, 943, 915, 875, 666; ^{1}H NMR: *δ* 1.01 and 1.19 (2s, 2×3H, C(8)Me_2), 1.77–1.89 and 1.96–2.06 (2 m, 2H, C(4)H_2), 2.29–2.44 (m, 2H, C(3)H_2), 2.77 (s, 1H, C(1)*H*), 4.35 (br d, *J* = 4.0 Hz, 1H, C(5)*H*), 4.85 and 4.92 (2br s, 2×1H, =CH_2); ^{13}C NMR: *δ* 20.5 and 25.9 (C(8)Me_2), 24.9 and 25.6 (*C*(3) and *C*(4)), 42.6 (*C*(8)), 59.7 (*C*(1)), 85.6 (*C*(5)), 113.1 (=CH_2), 140.1 (*C*(2)), 177.2 (*C*(7)); EIMS: *m*/*z* (%) 167 [M$^+$] (22), 122 (22), 121 (19), 107 (100), 105 (18), 93 (21), 91 (46), 79 (58), 77 (19), 67 (12), 65 (10), 53 (8), 41 (15).

4.6. (1*R*,5*S*)-8,8-Dimethyl-2-methylene-6-oxabicyclo-[3.2.1]octane ((1*R*,5*S*)-(+)-karahana ether), (+)-6

DIBALH (1 M in hexane, 2.62 mL, 1 equiv.) was added to a solution of (+)-**5** (435.7 mg, 2.62 mmol) in toluene (13 mL) at −78°C. After stirring for 45 min at −78°C, freshly distilled pyridine (630 μL, 3 equiv.), followed by a solution of DMAP (350 mg, 1.1 equiv.) in toluene–CH_2Cl_2, 4:1 (7.5 mL) and freshly distilled Ac_2O (990 μL, 4 equiv.) were sequentially added. The mixture was stirred for 14 h allowing it to warm to rt. The reaction was then quenched with a 1:1 mixture of satd aq. NH_4Cl and satd aq. sodium–potassium tartrate and the mixture was stirred at rt for 15 min. After phase separation the aq. layer was extracted with Et_2O (×3). The organic layer was washed with satd aq. $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated, toluene being removed as its azeotrope with MeOH. Chromatographic purification (hexane-EtOAc, 95:5→90:10) of the residue afforded lactol–acetate **12** (425.3 mg, 82% yield); IR: *ν* 1720;.^{1}H NMR: *δ* 2.10), which was immediately submitted to the following step. Et_3SiH (415 μL, 2.5 equiv.) followed by $BF_3{\cdot}Et_2O$ (160 μL, 1.2 equiv.) was added to a solution of **12** (208.2 mg, 1.05 mmol) in dry CH_2Cl_2 (10 mL) at −78°C, and the solution was stirred for 30 min at the same temperature. Then, a further portion of reactants was added and the solution was stirred for an additional 30 min while warming to −60°C. The reaction was quenched with satd aq. $NaHCO_3$ and stirred at rt for 15 min. After phase separation, the aq. phase was extracted with CH_2Cl_2 (×3) and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated at room pressure. The residue was purified by chromatography on silica gel (petroleum ether–Et_2O, 95:5) and *the fractions were carefully evaporated at reduced pressure* (0°C, from 120 to 80 torr) to give (+)-karahana ether (+)-**6** as a colorless liquid (128 mg, 80% yield); $[\alpha]_D^{20}$ = +76.6 (*c* 0.88, CH_2Cl_2), [lit. $[\alpha]_D$ = −70.3 (*c* 1.02, pentane)[13] and $[\alpha]_D^{25}$ = −68.0 (*c* 1.0, pentane)[14] for (−)-**6**]; IR (neat): *ν* 3071, 2983, 2939, 2877, 1647, 1494, 1454, 1388, 1368, 1286, 1226, 1174, 1148, 1066, 1035, 1018, 979, 937, 924, 911, 888, 799, 775, 738; ^{1}H NMR: *δ* 0.97 and 1.10 (2s, 2×3H, C(8)Me_2), 1.61–1.81 (m, 2H, C(4)H_2), 2.13 (dd, *J* = 6.6, 15.4 Hz, 1H, *H*C(3)H), 2.33 (d, *J* = 4.6 Hz, 1H, C(1)*H*), 2.35–2.50 (m, 1H, HC(3)*H*), 3.77 (d, *J* = 3.7 Hz, 1H, C(5)*H*), 3.82 (1H, d, *J* = 8.1 Hz, 1H, HC(7)*H*), 4.04 (dd, *J* = 4.6, 8.1 Hz, 1H, *H*C(7)H), 4.57 and 4.66 (2×1H, 2 br s, =CH_2); ^{13}C NMR: *δ* 20.8 and 25.4 (Me_2C(8)), 25.7 and 28.5 (*C*(3) and *C*(4)), 42.2 (*C*(8)), 53.9 (*C*(1)), 71.1 (*C*(7)), 82.3 (*C*(5)), 107.4 (=CH_2), 148.9 (*C*(2)); EIMS: *m*/*z* (%) 152 [M$^+$] (8), 135 (8), 122 (25), 121 (51), 120 (28), 107 (100), 105 (15), 95 (21), 93 (29), 91 (41), 81 (28), 79 (68), 77 (21), 67 (32), 53 (12), 43 (18), 41 (31).

4.7. (1′*R*,3′*S*)-*cis*-(3′-Hydroxy-2′,2′-dimethyl-6′-methylene-1′-cyclohexyl)methanol ((2*S*,6*R*)-(+)-*cis*-2-hydroxy-γ-cyclogeraniol), (+)-11

A solution of $LiAlH_4$ in THF (1 M, 8.33 mL, 2.5 equiv.) was added to a solution of (+)-**7** (660 mg, 3.33 mmol) in dry THF (30 mL) at 0°C and the mixture was stirred at 0°C for 2 h. The reaction was then quenched by cautious and sequential addition of H_2O (315 μL),15% aq. NaOH (475 μL) and again H_2O (315 μL) while vigorously stirring at 0°C for 5 min after each addition. The mixture was filtered on a glass Buchner funnel and the solid was abundantly washed with Et_2O; the resulting solution was then dried over Na_2SO_4 and evaporated. Filtration of the residue through a pad of silica gel with hexane–EtOAc, 1:2, gave diol (+)-**11** as a colorless solid (560 mg, 99% yield), mp 71–74°C; $[\alpha]_D^{20}$ = +46.6 (*c* 1.02, CH_2Cl_2), [lit.[14] $[\alpha]_D$ = −54.0 (*c* 1.0, $CHCl_3$) for (−)-**11**]; IR (KBr): *ν* 3315, 2936, 2876, 1651, 1482, 1455, 1363, 1291, 1256, 1200, 1134, 1097, 1029, 1010, 987, 958, 925, 883, 859, 782, 675; ^{1}H NMR: *δ* 0.97 and 1.02 (2s, 2×3H, Me_2C(2′)), 1.60–1.71 and 1.82–1.94 (2m, 2×1H, C(4′)H_2), 2.01 (dd, *J* = 7.3, 3.3 Hz, 1H, C(1′)*H*), 2.05–2.15 (m, 1H, C(5′)*H*), 2.45–2.58 (m, 3H, C(5′)*H*′ and 2×O*H*), 3.45–3.49 (m, 1H, C(3′)*H*), 3.71 (dd, A part of an ABX system, *J* = 10.8, 3.3, 1H, *H*C(1)HOH), 3.94 (dd, B part of an ABX system, *J* = 10.8, 7.3, 1H, HC(1)*H*OH); 4.76 and 4.95 (2s, 2×1H, =CH_2); ^{13}C NMR: *δ* 21.3 and 27.7 (Me_2C(2′)), 29.2 and 30.6 (*C*(4′) and *C*(5′)), 38.7 (*C*(2′)), 54.7 (*C*(1′)), 62.7 (*C*(1)), 74.1 (*C*(3′)), 110.3 (=CH_2), 148.0 (*C*(6′)); EIMS: *m*/*z* (%) 152 [M$^+$-H_2O] (5), 135 (4), 122 (50), 121 (40), 107 (100), 95 (21), 93 (32), 91 (37), 81 (42), 79 (70), 67 (50), 55 (20), 43 (43),

41 (38).). Anal. calcd for $C_9H_{18}O_2$: C, 70.55; H, 10.66; O,18.88. Found: C, 70.87; H, 10.43%.

4.8. (1′*R*,3′*S*)-*cis*-(3′-Hydroxy-2′,2′-dimethyl-6′-methylene-1′-cyclohexyl)methyl 2,2-dimethylpropionate ((2*S*,6*R*)-(−)-*cis*-2-hydroxy-γ-cyclogeranil pivaloate), (−)-18

DMAP (38.6 mg, 0.1 equiv.), followed by PivCl (421 mg, 1.1 equiv.) were added to a solution of (+)-**11** (538 mg, 3.16 mmol) in a 1:1 mixture of CH_2Cl_2–pyridine (30 mL) at 0°C and the mixture was stirred for 1 h at this temperature. TLC analysis of the mixture revealed the presence of compounds **18** and **19** in a ratio of ca. 7:3. The solution was then allowed to warm to 25°C and kept at this temperature for an additional 18 h. The reaction was then quenched with a few drops of MeOH and the solution was washed with satd aq. $NaHCO_3$. The aq. phase was extracted with CH_2Cl_2 (×2) and the combined organic layers were sequentially washed with satd aq. $NaHSO_4$ (×3), satd aq. $NaHCO_3$ (×2) and brine, dried over Na_2SO_4 and evaporated. Chromatographic purification of the residue on silica gel (hexane–EtOAc, 95:5→80:20) gave, in order of elution, 90 mg of dipavaloate of diol **11** (^{1}H NMR: δ 0.95 and 1.05 (2s, 2×3H, Me_2C(2′)), 1.20 and 1.27 (2s, 2×9H, 2′Bu), 1.61–1.72 and 1.77–1.90 (2m, 2×1H, C(4′)H_2), 2.05–2.16 (m, 1H, C(5′)*H*), 2.25 (dd, J=10, 3.5 Hz, 1H, C(1′)*H*), 2.30–2.45 (m, 1H, C(5′)*H*′), 4.25 (dd, J=10, 3.5 Hz, 1H, C(1)*H*), 4.50 (t, J=10 Hz, 1H, C(1)*H*′), 4.70 (m, 1H, C(3′)*H*), 4.68 and 4.90 (2br s, 2×1H, =CH_2), 15.6 mg of ester **19** (^{1}H NMR: δ 0.91 and 1.02 (2s, 2×3H, Me_2C(2′)), 1.43 (dd, J=10, 2.5 Hz, 1H, O*H*), 1.25 (s, 3H, ′Bu), 1.64–1.76 and 1.80–1.92 (2m, 2×1H, C(4′)H_2), 2.05–2.18 (m, 2H, C(1′)*H* and C(5′)*H*), 2.31–2.41 (m, 1H, C(5′)*H*′), 3.75 (td, J=10, 3.7 Hz, 1H, C(1)*H*), 3.88 (td, J=10, 2.5 Hz, 1H, C(1)*H*′), 4.71 (m, 1H, C(3′)*H*), 4.83 and 5.03 (2br s, 2×1H, =CH_2), and 562 mg (70% yield) of pivaloate (−)-**18** as a colorless oil; $[\alpha]_D^{20}=-7.2$ (c 0.91, CH_2Cl_2); IR (neat): ν 3504, 3071, 2975, 2939, 2872, 1727, 1709, 1648, 1481, 1459, 1398, 1365, 1289, 1163, 1117, 1077, 1027, 1010, 997, 955, 891, 857, 772; ^{1}H NMR: δ 0.88 and 1.09 (2s, 2×3H, Me_2C(2′)), 1.18 (s, 9H, ′Bu), 1.51–1.64 and 1.82–1.93 (2m, 2×1H, C(4′)H_2), 2.02–2.18 (m, 2H, C(1′)*H* and C(5′)*H*), 2.30 (br s, 1H, O*H*), 2.37–2.47 (m, 1H, C(5′)*H*′), 3.48 (dd, J=8.4, 3.9 Hz, 1H, C(3′)*H*), 4.34–4.38 (m, 2H, C(1)H_2), 4.63 and 4.90 (2s, 2×1H, =CH_2); ^{13}C NMR: δ 17.4 and 25.9 (Me_2C(2′)), 27.0 (Me_3C)), 30.9 and 31.3 (C(4′) and C(5′)), 38.6 and 39.2 (C(2′) and Me_3C), 50.6 (C(1′)), 62.4 (C(1)), 76.0 (C(3′)), 109.6 (=CH$_2$), 145.4.0 (C(6′)), 178.6 (′BuCO$_2$); EIMS: m/z (%) 254 [M$^+$] (1), 163 (1), 152 (18), 137 (18), 134 (38), 121 (22), 119 (62), 110 (26), 109 (23), 107 (30), 95 (18), 93 (23), 91 (21), 81 (21), 79 (33), 67 (28), 57 (100), 43 (24), 41 (72). HRMS calcd for $C_{13}H_{26}O_3$ 254.1882, found 254.1885.

4.9. (1′*R*,3′*S*)-*cis*-(3′-Imidazoylthiocarbonyloxy-2′,2′-dimethyl-6′-methylene-1′-cyclohexyl)methyl 2,2-dimethylpropionate ((2*S*,6*R*)-*cis*-2-imidazoylthiocarbonyloxy-γ-cyclogeranil pivaloate), 20

1,1′-Thiocarbonyldiimidazole (90% purity, 910 mg, 2.2 equiv.) was added to a solution of pivaloate (−)-**18** (532.6 mg, 2.09 mmol) in dry toluene (20 mL) and the mixture was heated under reflux for 14 h. Then H_2O was added and the aq. phase was extracted with hexane (×3); the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. Silica gel chromatography of the residue (hexane–EtOAc, 8:2→6:4) gave ester **20** as an oil (702.0 mg, 92% yield); IR (neat): ν 3080, 2971, 2871, 1725, 1652, 1479, 1385, 1320, 1283, 1231, 1155, 1103, 1035, 1011, 979, 961, 901, 833. ^{1}H NMR: δ 1.05 and 1.16 (2s, 2×3H, Me_2C(2′)), 1.20 (s, 9H, ′Bu), 1.80–1.92 (m, 1H, C(4′)*H*), 2.06–2.26 (m, 2H, C(4′)*H*′ and C(5′)*H*), 2.35 (dd, J=4.2, 9.3 Hz, 1H, C(1′)*H*), 2.39–2.49 (1H, m, C(5′)*H*′), 4.34 (dd, J=4.2, 11.1 Hz, 1H, C(1)*H*), 4.44 (dd, J=9.3, 11.1 Hz, 1H, C(1)*H*′), 4.76 and 5.00 (2s, 2×1H, =CH_2), 5.50 (dd, J=7.9, 3.8 Hz, 1H, C(3′)*H*), 7.09, 7.67, 8.41 (3s, 3×1H, Im); ESI-MS: m/z (%) 751 [2M+Na$^+$] (93), 729 [2M+H$^+$] (14), 387 [M+Na$^+$] (100), 365 [M+H$^+$] (46), 259 (6), 203 (9), 161 (9), 135 (21). Anal. calcd for $C_{19}H_{28}N_2O_3S$: C, 62.61; H, 7.74; N, 7.69; O, 13.17; S, 8.80. Found: C, 62.55; H, 7.81; N, 7.59%.

4.10. (*S*)-(2′,2′-Dimethyl-6′-methylene-1′-cyclohexyl)-methanol ((*S*)-(+)-γ-cyclogeraniol), (+)-16

Bu_3SnH (1.3 mL, 3 equiv.) and catalytic AIBN were added to a solution of thiocarbonate **20** (602 mg, 1.65 mmol) in oxygen free dry toluene (17 mL) and the mixture was heated under reflux for 8 h; then, two additional equivalents of Bu_3SnH and more catalytic AIBN were added and the mixture was refluxed for further 18 h. The mixture was then cooled to 0°C and excess $LiAlH_4$ (1 M in THF) was added. After 1.5 h at 0°C satd aq. NH_4Cl was added; the mixture was diluted with Et_2O and 1 M HCl was added until two clear phases were obtained. They were separated, the aq. phase was extracted with Et_2O (×3), and the organic layer was washed with satd aq. $NaHCO_3$ and brine. Excess DBU and a solution of I_2 in Et_2O were then added up to persistence of a pale yellow color in order to allow precipitation of tin salts.[29] The mixture was filtered through a silica pad and washed with Et_2O. Finally, the filtrate was washed in the order with satd aq. $Na_2S_2O_3$, satd aq. $CuSO_4$, and brine, dried ($MgSO_4$) and evaporated at room pressure. Silica gel chromatography of the residue (hexane–Et_2O, 98:2→90:10 for (+)-**16** and then 7:3→50:50 for (+)-**11**) and *evaporation of the fractions at room temperature* afforded 36.5 mg (13% yield) of diol (+)-**11** (*S*)-γ-cyclogeraniol (+)-**16** as colorless oil (190.8 mg, 75% yield); $[\alpha]_D^{20}=+24.9$ (c= 0.73, CH_2Cl_2), [lit. $[\alpha]_D^{20}=+24.5$ (c 0.03, $CHCl_3$)[7] and $[\alpha]_D^{21}=+23.7$ (c 0.31, $CHCl_3$)[30]]; IR (neat): ν 3385, 3070, 2931, 2867, 1647, 1479, 1385, 1365, 1159, 1067, 1029, 975, 945, 888, 848. ^{1}H NMR: δ 0.89 and 0.97 (2s, 2×3H, Me_2C(2′)), 1.24–1.65 (m, 5H, C(3′)H_2, C(4′)H_2, O*H*), 2.06 (dd, J=10.8, 4.9 Hz, 1H, C(1′)*H*), 2.13 (t, J=6.4 Hz, 2H, C(5′)H_2), 3.60–3.77 (m, 2H, C(1)H_2), 4.78 and 4.98 (2 br s, 2×1H, =CH_2); ^{13}C NMR: δ 26.4 and 28.4 (Me_2C(2′)), 23.0, 28.4, and 36.3 (C(3′), C(4′) and C(5′)), 33.8 (C(2′)), 56.3 (C(1′)), 59.5 (C(1)), 111.5 (=CH$_2$), 147.4 (C(6′)); EIMS: m/z (%) 154 [M$^+$] (4), 136

(30), 123 (39), 121 (61), 109 (32), 107 (25), 95 (38), 93 (97), 91 (36), 81 (100), 79 (65), 77 (30), 69 (89), 67 (68), 55 (22), 41 (77).

4.11. (*S*)-2′,2′-Dimethyl-6′-methylene-1′-cyclohexylcarbaldehyde ((*S*)-(+)-γ-cyclocitral), (+)-13

A solution of DMSO (92 μL, 2.5 equiv.) in dry CH_2Cl_2 (2.5 mL) was added to a solution of freshly distilled $(COCl)_2$ (68 μl, 1.5 equiv.) in dry CH_2Cl_2 (6 mL) at −78°C. After 15 min at −78°C, a solution of γ-cyclogeraniol (+)-**16** (80.0 mg, 0.518 mmol, 1 equiv.) in dry CH_2Cl_2 (4 mL) was added. After 30 min at −78°C, freshly distilled Et_3N (325 μL, 4.5 equiv.) was added and the mixture was stirred for 3 h while warming to room temperature. The reaction was then quenched with H_2O; after extraction with CH_2Cl_2 (× 3), the combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel (pentane–Et_2O, 95:5) and *careful evaporation of the fractions at room temperature* afforded of the readily epimerizable aldehyde (+)-**13**, as a colorless oil (64.0 mg, 86%), which was immediately submitted to the following step; IR (neat): *ν* 3077, 2935, 2870, 2722, 1722, 1688, 1644, 1454, 1388, 1367, 1211, 1159, 988, 896; ^{1}H NMR: *δ* 0.98 and 1.09 (2×3H, 2s, Me_2C(2′)), 1.36–1.45 and 1.58–1.73 (2m, 1H, 3H, C(3′)H_2 and C(4′)H_2), 2.17–2.26 (m, 2H, C(5′)H_2), 2.69 (d, J=4 Hz, 1H, C(1′)H), 4.72 and 4.97 (2s, 2×1H, =CH_2), 9.87 (d, 1H, J=4 Hz, C(1)H); ^{13}C NMR: *δ* 25.9 and 28.0 (Me_2C(2′)), 22.7, 33.3, and 37.4 (*C*(3′), *C*(4′), and *C*(5′)), 34.8 (*C*(2′)), 66.4 (*C*(1′)), 112.3 (=*C*H_2), 143.4 (*C*(6′)), 203.1 (*C*(1)); EIMS: *m*/*z* (%) 152 [M$^+$] (3), 137 (18), 123 (41), 121 (17), 109 (73), 107 (15), 95 (43), 94 (35), 93 (21), 91 (21), 81 (100), 79 (45), 77 (20), 69 (39), 67 (58), 53 (16), 41 (51).

4.12. (*S*)-(*E*)-4-(2′,2′-Dimethyl-6′-methylene-1′-cyclohexyl)-but-3-en-2-one ((*S*)-(+)-γ-ionone), (+)-3

Diethyl (2-oxopropyl)phosphonate (225 μL, 1.12 mmol, 3 equiv.) was added to a suspension of finely pulverized $Ba(OH)_2{\cdot}8H_2O$ (71 mg, 0.224 mmol, 0.6 equiv.) in THF (3.6 mL) at room temperature and the mixture was stirred for 30 min; a solution of (+)-**13** (57.0 mg, 0.374 mmol) in THF–H_2O 40:1 (3.6 mL) was then added and stirring was continued at room temperature for an additional 15 h. After dilution with CH_2Cl_2, the mixture was washed with H_2O; the aq. phase was extracted with CH_2Cl_2 (×3) and the combined organic layers were washed with satd aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel (pentane-Et_2O, 98:2→90:10) gave 59.6 mg (83% yield, GC purity=98.3%) of (*S*)-γ-ionone (+)-**3** as a colorless oil with a fine and distinct violet scent; $[\alpha]_D^{20}$=+30.3 (*c* 1.1, CH_2Cl_2), [lit.[6] $[\alpha]_D^{20}$=+36.2 (*c* 1, $CHCl_3$) and $[\alpha]_D^{20}$=+30.2 (*c* 0.5, EtOH)]; 88% e.e. (enantioselective GC on a DAcTBuSilBETACDX column; He gas carrier, 1 mL/min; split ratio=1:50; temperature program=80°C(0 min)→2°C/min→150°C; t_R=32.7 min for (−)-**3**, t_R=33.1 min for (+)-**3**);. IR (neat): *ν* 3078, 2931, 2867, 1697, 1675, 1644, 1625, 1460, 1438, 1386, 1364, 1253, 1231, 1177, 991, 890; ^{1}H NMR: *δ* 0.86 and 0.91 (2s, 2×3H, Me_2C(2′)), 1.29–1.41 and 1.45–1.65 (2m, 1H and 3H, C(3′)H_2 and C(4′)H_2), 2.00–2.12 and 2.19–2.33 (2m, 2×1H, C(5′)H_2), 2.27 (3H, s, C(1)H_3), 2.58 (d, J=10.0 Hz, 1H, C(1′)H), 4.54 and 4.79 (2s, 2×1H, =CH_2), 6.09 (d, J=15.8 Hz, 1H, C(3)H), 6.93 (dd, J=15.8, 10.0 Hz, 1H, C(4)H); ^{13}C NMR: *δ* 24.3 and 27.6 (Me_2C(2′)), 29.6 (*C*(1)), 23.5, 34.5, and 39.0 (*C*(3′), *C*(4′), and *C*(5′)), 35.9 (*C*(2′)), 57.9 (*C*(1′)), 110.0 (=*C*H_2), 133.1 (*C*(3)), 133. 1 (*C*(4)), 148.7 (*C*(6′)), 198.6 (*C*(2)); EIMS: *m*/*z* (%) 192 [M$^+$] (9), 177 (12), 164 (11), 159 (11), 149 (100), 135 (12), 131 (11), 121 (53), 109 (45), 107 (21), 93 (28), 91 (36), 81 (43), 79 (35), 77 (31), 69 (41), 67 (21), 65 (20), 53 (11), 43 (78), 41 (43).

4.13. (1′*S*,1*RS*)-1-(2′,2′-Dimethyl-6′-methylene-1′-cyclohexyl)-but-3-en-1-ol, 22A–B

Allyltributyltin (480 μL, 3 equiv.) was added to a solution of aldehyde (+)-**13** (78.7 mg, 0.517 mmol) in dry CH_2Cl_2 (7 mL) at −78°C; after 2 min, $BF_3{\cdot}Et_2O$ (65 μL, 1 equiv.) was added dropwise over 3 min and the mixture was stirred at −78°C for 30 min. The reaction was then quenched with satd aq. $NaHCO_3$ and the aq. phase was extracted with CH_2Cl_2 (×3). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel (pentane–ether, 98:2→95:5) furnished **22A** (47 mg), contaminated by tin residues, followed by adduct **22B** (38 mg); **22A**:**22B**=56:44 by GC. Adduct **22A** (undetermined stereochemistry at C-1): ^{1}H NMR: *δ* 0.96 and 1.06 (2s, 2×3H, Me_2C(2′)), 1.16–1.76 (m, 4H, C(3′)H_2 and C(4′)H_2), 1.88 (td, J= 13.1, 4.7 Hz, 1H, HC(5′)H); 2.11–2.21 and 2.22–2.33 (2m, 2H and 2H, C(1′)H, HC(5′)H, C(2)H_2), 3.91–3.99 (m, 1H, C(1)H), 4.60 and 4.91 (2s, 2×1H, =CH_2), 5.10 (A part of an ABX system, 1H, C(4)HH), 5.15 (B part of an ABX system, 1H, C(4)HH), 5.78–5.92 (X part of an ABX system, 1H, C(3)H); EIMS: *m*/*z* (%) 194 [M$^+$] (1), 176 (12), 161 (6), 153 (4), 135 (11), 125 (15), 124 (12), 123 (11), 109 (100), 95 (22), 93 (7), 91 (6), 81 (19), 79 (9), 77 (4), 69 (16), 67 (21), 55 (4), 53 (4), 43 (10), 41 (20).

Adduct **22B** (undetermined stereochemistry at C-1): IR (neat): *ν* 3444, 3071, 2976, 2931, 2868, 1645, 1462, 1443, 1387, 1365, 1343, 1281, 1205, 1161, 1116, 1066, 1034, 995, 987, 911, 891, 867, 67; ^{1}H NMR: *δ* 0.94 and 1.11 (2s, 2×3H, Me_2C(2′)), 1.23–1.82 (m, 5H, C(3′)H_2, C(4′)H_2, 1 allylic H), 1.88 (d, J=8.1 Hz, 1H, allylic H), 1.94–2.07 (m, 1H, allylic H), 2.12–2.30 (2m, 2H, C(1′)H, HC(5′)H), 3.83–3.91 (m, 1H, C(1)H), 4.67 and 4.81 (2s, 2×1H, =CH_2), 5.15 (A part of an ABX system, 1H, C(4)HH), 5.18 (B part of an ABX system, 1H, C(4)HH), 5.81–5.95 (X part of an ABX system, 1H, C(3)H); EIMS: *m*/*z* (%) 194 [M$^+$] (1), 176 (9), 161 (6), 153 (3), 135 (7), 125 (12), 124 (14), 123 (11), 109 (100), 95 (15), 93 (8), 91 (8), 81 (23), 79 (9), 77 (5), 69 (15), 67 (22), 55 (6), 43 (12), 41 (23). HRMS calcd. for $C_{13}H_{22}O$ 194.1671, found 194.1668.

4.14. (*S*)-1-(2′,2′-Dimethyl-6′-methylene-1′-cyclohexyl)-but-3-en-1-one, (+)-23

Dess–Martin periodinane[27] (265 mg, 1.2 equiv.) was added to a solution of adducts **22A** and **22B** (100.2 mg, 0.51 mmol) in CH_2Cl_2 (14 mL) at room temperature and the mixture was stirred for 1.5 h. Then, a 1:1 mixture of satd aq. $NaHCO_3$ and satd aq. $Na_2S_2O_3$ was added and stirring was continued until a clear mixture was obtained (10 min). The aq. phase was extracted with CH_2Cl_2 (×3) and the combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. Chromatography of the semisolid residue on silica gel (pentane–Et_2O, 25:1) afforded product (+)-**23** as colorless and odorless oil (70.8 mg, 71% overall yield from aldehyde **13**); $[\alpha]_D^{20}=+290$ (*c* 1.1, CH_2Cl_2); IR (neat): *v* 3075, 2945, 2868, 1713, 1642, 1439, 1387, 1365, 1345, 1234, 1156, 1131, 1068, 1043, 992, 918, 894, 861, 765, 733; ^{1}H NMR: δ 0.89 and 0.95 (2s, 2×3H, Me_2C(2′)), 1.13–1.23, 1.44–1.57 and 1.58–1.69 (3m, 3×1H, C(3′)H_2 and C(4′)*H*H), 1.98 (td, $J=12.4$, 4.4 Hz, 1H, C(4′)H*H*), 2.08 (dt, $J=13.4$, 4.4 Hz, 1H, C(5′)*H*H), 2.22 (td, $J=13.4$, 5.2 Hz, 1H, C(5′)H*H*), 3.11 (s, 1H, C(1′)*H*), 3.11–3.33 (m, 2H, C(2)H_2), 4.73 and 4.88 (2s, 2×1H, =CH_2), 5.10 (A part of an ABX system, 1H, C(4)*H*H), 5.17 (B part of an ABX system, 1H, C(4)H*H*), 5.81–5.96 (X part of an ABX system, 1H, C(3)*H*); ^{13}C NMR: δ 27.2 and 27.5 (Me_2C(2′)), 22.8, 31.5, and 35.2 (*C*(3′), *C*(4′), and *C*(5′)), 34.9 (*C*(2′)), 48.8 (*C*(2)), 65.5 (*C*(1′)), 112.0 (=CH_2), 118.5 (*C*(4)), 130.7 (*C*(3)), 145.2 (*C*(6′)), 208.1 (*C*(1)); EIMS: *m*/*z* (%) 192 [M$^+$] (3), 149 (2), 135 (3), 123 (100), 109 (4), 95 (6), 93 (3), 91 (3), 82 (11), 81 (38), 79 (11), 67 (12), 55 (3), 53 (3), 41 (19). HRMS calcd for $C_{13}H_{20}O$ 192.1514, found 192.1511.

4.15. (*S*)-(*E*)-1-(2′,2′-Dimethyl-6′-methylene-1′-cyclohexyl)-but-2-en-1-one ((*S*)-(+)-γ-damascone), (+)-4

DBU (33 μL, 0.5 equiv.) was added to a solution of (+)-**23** (64.0 mg, 0.333 mmol) in dry CH_2Cl_2 (3.5 mL) at room temperature and stirring was continued for 7 h. Satd aq. $CuSO_4$ was added and the aq. phase was extracted with CH_2Cl_2 (×3); the combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. Filtration of the residue through a silica gel pad by eluting with pentane–Et_2O, 95:5, afforded (*S*)-γ-damascone) (+)-**4** as a pleasantly fruity-floral perfumed colorless oil (57.6 mg, 90% yield, GC purity ≥98%, *E*:*Z*=24.4:1) of; $[\alpha]_D^{20}=+230$ (*c* 1.40, CH_2Cl_2), (lit.[7] $[\alpha]_D^{20}=+259$); e.e.=87.5% {enantioselective HPLC on a Daicel Chiralcel® OD column, 4.6×250 mm; solvent=hexane–*i*-PrOH, 500:1; flow=0.9 mL/min; detector: 254 nm; $t_R=12.9$ min for (+)-**4**, $t_R=14.5$ min for (−)-**4**); IR (neat): *v* 3072, 3037, 2943, 2867, 1693, 1667, 1629, 1474, 1443, 1385, 1364, 1347, 1324, 1293, 1279, 1233, 1185, 1156, 1124, 1075, 1047, 967, 943, 894, 873, 835, 795, 777, 736, 671, 639; ^{1}H NMR: δ 0.92 and 0.96 (2s, 2×3H, Me_2C(2′)), 1.21 (dt, $J=13.4$, 4.6 Hz, 1H, C(3′)H_{eq}), 1.45–1.71 (m, 2H, C(3′)H_{ax} and C(4′)H_{eq}), 1.88 (dd, $J=6.9$, 1.8 Hz, 3H, C(4)H_3), 2.00 (m, 1H, C(4′)H_{ax}), 2.10 (dt, $J=13.4$, 4.8 Hz, 1H, C(5′)H_{eq}), 2.29 (td, $J=13.4$, 5.2 Hz, 1H, C(5′)H_{ax}), 3.22 (s, 1H, C(1′)*H*), 4.70 and 4.86 (2 br s, 2×1H, =CH_2), 6.18 (dq, $J=15.5$, 1.8 Hz, 1H, C(2)*H*), 6.86 (dq, $J=15.5$, 6.9 Hz, 1H, C(3)*H*); ^{13}C NMR: δ 29.6 (*C*(4)), 26.6 and 27.7 (Me_2C(2′)), 22.8, 31.9, and 35.7 (*C*(3′), *C*(4′), and *C*(5′)), 34.9 (*C*(2′)), 63.7 (*C*(1′)), 111.7 (=CH_2), 132.7 (*C*(2)), 141.5 (*C*(3)), 145.2 (*C*(6′)), 199.4 (*C*(1));. EIMS: *m*/*z* (%) 192 [M$^+$] (12), 177 (5), 159 (2), 149 (5), 136 (4), 135 (5), 123 (8), 122 (12), 121 (10), 109 (8), 107 (7), 93 (8), 91 (9), 81 (16), 79 (11), 77 (8), 69 (100), 67 (10), 43 (8), 41 (38).

Acknowledgements

We thank the Italian CNR, MURST (funds COFIN), and the University of Pavia (funds FAR) for financial support, and Professor Mariella Mella and Professor Giorgio Mellerio for NMR and MS spectra, respectively.

References

1. Ohloff, G. *Scent and Fragrances*: *The Fascination of Fragrances and their Chemical Perspectives*; Springer-Verlag: Berlin, 1994.
2. Pybus, D. H.; Sell, C. S. *The Chemistry of Fragrances*; The Royal Society of Chemistry, 1999.
3. Eugster, C. H.; Buchecker, R.; Tscharner, C.; Uhde, G.; Ohloff, G. *Helv. Chim. Acta* **1969**, *52*, 1729–1731.
4. Buchecker, R.; Egli, R.; Regel-Wild, H.; Tscharner, C.; Eugster, C. H.; Uhde, G.; Ohloff, G. *Helv. Chim. Acta* **1973**, *56*, 2548–2563.
5. Oritani, T.; Yamashita, K. *Agric. Biol. Chem.* **1987**, *51*, 1271–1275.
6. Fuganti, C.; Serra, S.; Zenoni, A. *Helv. Chim. Acta* **2000**, *83*, 2761–2768.
7. Fehr, C.; Galindo, J. *Helv. Chim. Acta* **1995**, *78*, 539–552.
8. Armstrong, R. J.; Weiler, L. *Can. J. Chem.* **1983**, *61*, 214–215.
9. Armstrong, R. J.; Weiler, L. *Can. J. Chem.* **1986**, *64*, 584–596.
10. Vidari, G.; Dapiaggi, A.; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485–6488.
11. Vidari, G.; Lanfranchi, G.; Masciaga, F.; Meriggi, J.-D. *Tetrahedron: Asymmetry* **1996**, *7*, 3009–3020.
12. Stork, G.; Doi, T.; Liu, L. *Tetrahedron Lett.* **1997**, *38*, 7471–7474.
13. Mori, K.; Mori, H. *Tetrahedron* **1985**, *41*, 5487–5493.
14. Galano, J. M.; Audran, G.; Monti, H. *Tetrahedron* **2000**, *56*, 7477–7481.
15. Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317–8320.
16. Naya, Y.; Kotake, M. *Tetrahedron Lett.* **1968**, 1645–1649.
17. Audran, G.; Galano, J. M.; Monti, H. *Eur. J. Org. Chem.* **2001**, 2293–2296.
18. Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem.* **1981**, *53*, 15–31.
19. Corey, E. J.; Luo, G.; Lin, L. S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1126–1128.
20. Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324–2335.

21. Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148–4150 and references cited therein.
22. Paterson, J.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774–776.
23. Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295–1298.
24. Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1–22.
25. Nishigaichi, Y.; Takuwa, A.; Naruta, Y.; Maruyama, K. *Tetrahedron* **1993**, *49*, 7395–7426.
26. Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293.
27. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
28. Schulte-Elte, K. H.; Rautenstrauch, V.; Ohloff, G. *Helv. Chim. Acta* **1971**, *54*, 1805–1812.
29. Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140–3157.
30. Tanimoto, H.; Oritani, T. *Tetrahedron* **1997**, *53*, 3527–3536.